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PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Serge Louis Boulet	Group Art Unit: 1625
Serial No.:	10/533,328	Examiner: Taofiq A. Solola, Ph.D., J.D.
Application Date:	10/24/2003	Conf No.: 5367
US Nat'l Entry Date (if applicable):	05/02/2005	
For:	3-Aryloxy/thio-2,3-substituted propanamines and their use in inhibiting serotonin and norepinephrine reuptake	
Docket No.:	X-15985	

REPLY UNDER 37 C.F.R. 1.111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper is in response to the Office Action dated November 29, 2007.

Status of the Claims

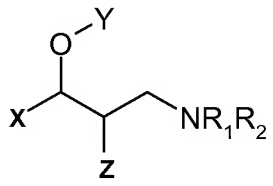
The Examiner has rejected claims 1, 5, and 31 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. 4,018,895 (Molloy) in view of U.S. 5,776,969 (James) and Med Chem: Principles and Practice, 206 – 208 (1994) (King). The Examiner has also provisionally rejected claims 1, 5, and 31 on the ground of nonstatutory obviousness-type double patenting over claims 6-7, 22, and 34 of copending Application No. 10/532,765 in view of King.

Rejection Under 35 U.S.C. § 103(a)

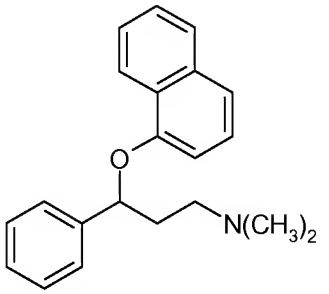
The Examiner has rejected claims 1, 5, and 31 under 35 U.S.C. § 103(a), reasoning that the differences between the presently claimed compounds and those of Molloy are merely bioisosteric replacements taught by James and King. At issue is whether the bioisosteric

relationship alone between the presently claimed compounds and those in the prior art renders the presently claimed compounds *prima facie* obvious. Applicants assert that the alleged bioisosteric relationship alone is not sufficient to support *prima facie* obviousness and, therefore, the rejection is improper. Reconsideration and withdrawal of the rejection and allowance of claims 1, 5, and 31 in view of the following discussion are respectfully requested.

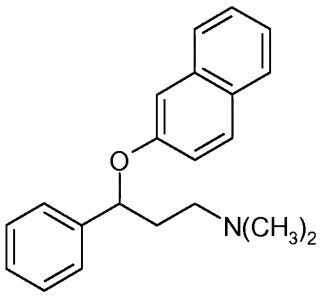
"[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." (*Takeda Chemical Industries Ltd. v. Alphapharm Pty, Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007)) Claim 1 of the present application encompasses compounds of the following formula:



where X is phenyl optionally substituted with fluorine, Y is benzothienyl optionally substituted with fluorine, Z is OH or F, R_1 and R_2 are each independently H or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof. Molloy exemplifies the following species:



Molloy A, Column 12, Table I: α-naphthyl



Molloy B, Column 12, Table I: β-naphthyl

relied upon by the Examiner. To arrive at compounds within the present application, the prior art must motivate the skilled artisan to both select the above compounds as a starting point for modification, and then suggest the two specific modifications: replacing a particular hydrogen atom with either hydroxy or fluoro; and replacing one –CH=CH- moiety on the naphthyl ring with a sulfur atom. In the absence of either of these elements, the finding of *prima facie* obviousness is improper. ["The court properly concluded that Alphapharm did not make out a *prima facie* case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to

perform the chemical modifications necessary to achieve the claimed compounds." (*Id.* at 1179)]

As a threshold matter, the Examiner has simply failed to explain why the skilled artisan would select Molloy A or Molloy B as a starting point for modification. This failure alone is sufficient to defeat a finding of *prima facie* obviousness. (*Id.*) Furthermore, reliance on the general concept of bioisosterism to provide the requisite motivation to modify Molloy A or Molloy B, or any other prior art compound, to arrive at the presently claimed compounds is simply insufficient. The classical isosteres taught by King are **not** suggested as bioisosteric as the Examiner suggests, rather they are isosteric replacements that "only become bioisosteric if biological activity is retained." (King, page 207, last paragraph, first sentence) Clearly, one would first need to prepare the compounds to determine whether the activity had been retained before the moiety qualifies as a bioisostere to the one it replaced. Furthermore, King does not suggest that any of the proposed isosteric or bioisosteric replacements will predictably result in new compounds with similar biological properties. Quite to the contrary, King states:

> "When considering any approach to lead optimisation, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analysing the result of such replacements. For example, a simple CH_2 to O or S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pKa, metabolism, or hydrogen bonding capacity, all with unpredictable effects upon biological activity."

(King, page 209, emphasis added)

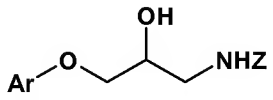
Applicants note that the Examiner relied only on pages 206 – 208 of King. The topic of BIOISOSTERIC REPLACEMENT in King includes page 209. Applicants respectfully submit that a reference must be considered as a whole. (*See*: M.P.E.P. § 2141.03(VI), "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.") A full copy of the BIOISOSTERIC REPLACEMENT section of King, including page 209, is provided with this paper for the Examiner's convenience.

The unpredictable nature of bioisosteric replacement described by King has been acknowledged in the case law as well. For example, the replacement of an oxygen atom in an ester moiety (-C(O)OR) with a sulfur atom was held not to render the resulting thioester (-C(O)SR) obvious even though the Court agreed that "it was not inconceivable to substitute [sulfur for oxygen] to obtain compounds having the same expected properties." (*In re Grabiak*, 226 USPQ 870, 872 (Fed. Cir. 1985)) The court held that "there must be adequate support in the prior art for the ester/thioester change in structure, in order to complete the PTO's *prima facie*

case and shift the burden of going forward to the applicant." (*Id.*) This prior art support cannot be limited to the suggestion that one moiety is similar to another in some respect, the prior art must suggest that the resulting molecules will have similar biological activities to establish *prima facie* obviousness. ("If evidence of similar biological properties between –C(O)OR and –C(O)SR groups is to be relied upon, it must come from the prior art." (*Id.*))

The Examiner also relies on *Merck* (*In re Merck*, 231 USPQ 375 (Fed. Cir. 1986) to support the premise that an isosteric relationship alone is sufficient to establish *prima facie* obviousness of a novel compound. The Examiner's interpretation of *Merck*, however, is simply incorrect. The alleged bioisosteric relationship alone between amitriptylene and imipramine was **not** sufficient to render the use of amitryptilene for the treatment of depression *prima facie* obvious. The structural similarity between amitriptylene and imipramine, in combination with technical reports suggesting that amitriptylene would also be useful for the treatment of depression, were required to establish *prima facie* obviousness. ("The expectation that the similar structures would behave similarly was suggested in the Roche Reports. In combination with those teachings, the prior art teaching that the precise structural difference between amitriptylene and imipramine involves a known bioisosteric replacement provides sufficient basis for the required expectation of success, without resort to hindsight." (*Id.* at 379); *See also*: M.P.E.P. § 2143.02(I)) As such, *Merck* is consistent with *In re Grabiak* in support of the proposition that bioisosterism alone is insufficient to support a finding of *prima facie* obviousness. ("The teachings of the Roche Reports as well as the Petersen reference distinguish this case from *In re Grabiak*." *Merck* at 380, Footnote 10, citation and quote omitted)

The Examiner also points to James to support the replacement of a naphthalene with a benzothiophene. James generically describes compounds of the following formula:



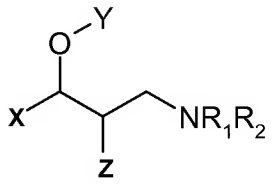
where variable Ar is defined to include both naphthalene and benzothiophene. This reference, however, considered in combination with Molloy, is insufficient to support a finding of *prima facie* obviousness. Even assuming that James teaches the equivalence of naphthalene and benzothiophene, compounds corresponding with the formula in James are taught to be serotonin 1a antagonists, not inhibitors of serotonin or norepinephrine reuptake. As such, James does not suggest that replacing the naphthalene of Molloy A or B with benzothiophene will result in a compound that retains norepinephrine and serotonin reuptake inhibitory activity. Furthermore, merely identifying substituents in the prior art that could be combined to arrive at novel

compounds is not the standard for obviousness, much more is required. "[M]ere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious. . . . Rather, to establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to make to select the references and to combine them in the particular claimed manner to reach the claimed invention." (*Eli Lilly and Company v. Zenith Goldline Pharmaceuticals, Inc.*, 81 USPQ2d 1324, 1331 (Fed. Cir. 2006))

Because the Examiner has not established why the skilled artisan would select any identified prior art compound for further modification and, because bioisosterism does not establish obviousness on its face, the finding of *prima facie* obviousness is not proper and must be withdrawn. Reconsideration and withdrawal of the rejection, and allowance of claims 1, 5, and 31 in view of the foregoing discussion.

Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1, 5, and 31 on the ground of nonstatutory obviousness-type double patenting over claims 6-7, 22, and 34 of copending Application No. 10/532,765 in view of King. Claim 1 of the present application encompasses compounds of the following formula:



where X is phenyl optionally substituted with fluorine, Y is benzothienyl optionally substituted with fluorine, Z is OH or F, R_1 and R_2 are each independently H or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof. Copending Application No. 10/532,765 differs in that variable Z is hydrogen and variable Y is thienopyridinyl. The Examiner relies solely on the information in King to support the obviousness of these claims relative to each other. As discussed in the preceding section, because bioisosterism, the sole basis offered in support of the obviousness conclusion, does not establish obviousness on its face, the finding of *prima facie* obviousness is not proper and must be withdrawn. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 5, and 31 in view of the foregoing discussion.

Defective Specification

The Examiner has required Applicants to provide a replacement specification in view of illegible portions in the application on file. A replacement specification accompanies this paper. Applicants assert that the replacement specification is a true copy of the application as originally filed. Entry of the replacement specification is respectfully requested.

Respectfully submitted,

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CHAPTER 14

Bioisosteres, Conformational Restriction, and Pro-drugs – Case History: An Example of a Conformational Restriction Approach

FRANK D. KING

1 INTRODUCTION

The primary role of the medicinal chemist in a research project team within the pharmaceutical industry is to assist in the identification of a target lead compound and then convert that compound into a potential development candidate for eventual marketing as a drug. The lead compound can come from a number of sources, for example cross screening, a natural substrate or receptor mediator, an already marketed drug or competitor compound, or finally a structure designed from *ab initio* considerations of the receptor or enzyme. By definition, the lead compound does not normally satisfy the requirement for development due to some shortcoming in its properties. This could be, for example, a lack of specificity, low potency, metabolic or chemical instability, acute toxicity, poor bioavailability, unsatisfactory solubility, or even simply lack of novelty, precluding the possibility of patent protection, or a combination of these factors.

Faced with this challenge, the medicinal chemist has to devise a research strategy to achieve this objective in the shortest possible time. Initial approaches that can be taken can be loosely categorised into 'non-rational' and 'rational'. In the 'non-rational', all simple, readily accessible variations of the lead compound are made based on simple chemistry with little or no regard to biological activity. This approach, though intellectually unattractive, can be very successful provided that a large number and variety of compounds can be both prepared and tested in a very short period of time. A large amount of retrospective SAR knowledge can be built up very quickly which can be subsequently used for more rational approaches. In addition, the 'art' of medicinal chemistry is still such that this approach frequently throws up new exciting leads which no rational approach would ever have identified! The ultimate extreme of this is the concept of 'combinatorial libraries' where large numbers of compounds are rapidly prepared and tested as mixtures.

Alternatively, or in addition, 'rational' approaches can be adopted at an early

stage. These approaches are particularly applicable to series of analogues which are difficult to synthesise and/or difficult to evaluate. One may adopt one or more approaches making the maximum possible use of SAR aids available. Some of these SAR aids have been covered in earlier QSAR and computational methodology chapters, but the experienced practitioner will frequently supplement these with more 'intuitive' approaches based on selective transformations of the molecule to probe the mechanism of binding and activation/inhibition. Thus, functionalities within the lead compound could be rationally altered based on hypotheses of, say, intermolecular binding or intramolecular conformation, and the results from like-for-like and like-for-non-like changes analysed and used for future target identification.

Three of the standard methodologies that the medicinal chemist can use as 'rational' approaches to lead optimisation form the basis of this chapter. These are bioisosteric replacement, conformational restriction, and pro-drug formation. The first topic has been covered in detail in a number of excellent reviews,[1,2] and therefore I shall only briefly touch on it here. Conformational restriction as a methodology for lead optimisation has been less comprehensively covered, and therefore I will examine this in more detail. The pro-drug approach is normally employed for optimisation of non-pharmacologically related properties such as pharmacokinetics, oral bioavailability, brain penetration *etc.* In the last section of the chapter I shall describe some of the work we, and others, have done using a conformational restriction approach to a weak, non-selective lead compound, metoclopramide, and as a result have identified potent and selective dopamine, 5-HT_3 and 5-HT_4 receptor antagonists and 5-HT_4 receptor agonists.

2 BIOISOSTERIC REPLACEMENT

Isosteres are substituents or groups which have the same size or volume. Bioisosteres, however, are substituents or groups that do not necessarily have the same size or volume, but have a similarity in chemical or physical properties which produce broadly similar biological properties. It is therefore unlikely that bioisosterism will produce marked increases in potency; however significant changes in selectivity, toxicity, and metabolic stability could be expected. Traditionally bioisosteres have been classified into two groups, *classical isosteres* which have approximately the same size, shape, and outer electronic configuration (Table 1) and *non-classical bioisosteres* which do not have the same number of atoms and do not fit the steric and electronic rules of the classical isososteres, but do produce similar biological activity (Table 2).

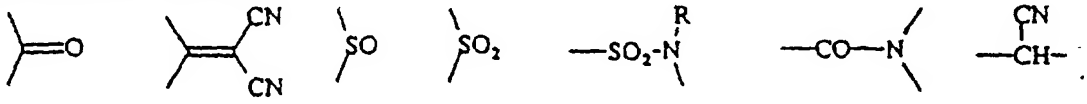
In general, *classical isosteric* replacement is *like-for-like* in terms of number of atoms, valency, degree of unsaturation, and aromaticity and only becomes a *bioisosteric* replacement if biological activity is retained. *Non-classical bioisosterism* retains activity by the retention of other properties such as pK_a, electrostatic potentials, HOMOs and LUMOs *etc.* for which modern computational analysis methodology can aid in rationalisation.

Table 1: *Classical isosteres which may function as bioisosteres*

Univalent atoms and groups	Bivalent
A. $-CH_3$; $-NH_2$; -OH; -F; -Cl	A. $-CH_2-$; -NH-; -O-; -S-; -Se-
B. -Cl; $-PH_2$; -SH	B. $-COCH_2-$; -CONH-; -COO-; -COS-
C. -Br; -i-Pr	**Trivalent** **Tetravalent**
D. -I; -t-Bu	A. -CH=; -N= A. >C<; >Si<
	B. -P=; -As= B. =C=; $=N^+=$; $=P^+=$
Ring equivalents	
A. -CH=CH-; -S-	(*e.g.* benzene, thiophene)
B. -CH=; -N=	(*e.g.* benzene, pyridine)
C. -O-; -S-; $-CH_2-$; -NH-	(*e.g.* tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

Table 2: *Non-classical bioisosteres*

CARBONYL GROUP

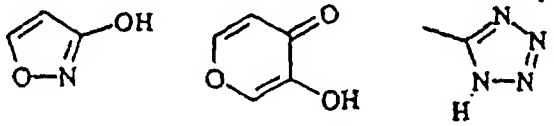


CARBOXYLIC ACID GROUP

COOH SO_2NHR SO_3H

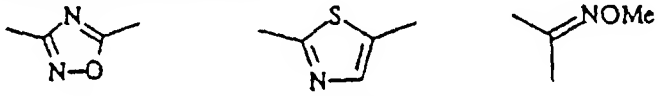
CONHCN CONHOH

PO(OH)OEt $PO(OH)NH_2$



CARBOXYLIC ESTER GROUP

-COO-



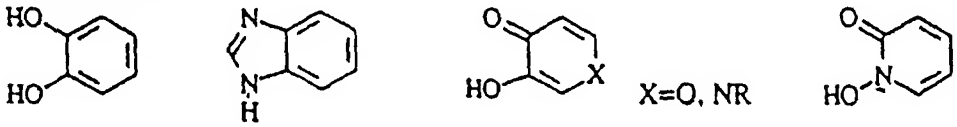
CARBOXYLIC AMIDE GROUP (IN PEPTIDES)

-CONH- -CONMe- -CSNH- $-CH_2NH-$ -NHCO- >C=C< $-CH_2S-$

HYDROXY GROUP

-OH -NHCOR $-NHSO_2R$ $-CH_2OH$ $-NHCONH_2$ -NHCN $-CH(CN)_2$

CATECHOL



X=O, NR

HALOGEN

HALOGEN CF_3 CN NCN_2 $C(CN)_3$

THIOUREA

$NHC(=S)NH_2$ $NHC(=NCN)NH_2$ $NHC(=CHNO_2)NH_2$

When considering any approach to lead optimisation, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analysing the result of such replacements. For example a simple CH_2 to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pK_a, metabolism, or hydrogen bonding capacity, all with unpredictable effects upon biological activity. In addition isosteric and bioisosteric replacement can give very useful information regarding the key interacting functionalities of the compound with the enzyme or receptor. For example if the primary interaction of a secondary amide is as a hydrogen bonding acceptor, replacement of the amide by ester, ketone, or tertiary amide may retain potency. However, if the primary interaction involves NH as a hydrogen bond donor, all these changes will probably result in reduced potency. Similarly if the amide group is non-interactive, simply a spacer, then many isosteric replacements frequently used for peptide bond stabilisation, for example $-CH_2NH-$, $-CH_2S-$, $-CH=CH-$ or even $-CH_2CH_2-$, may retain activity. A more detailed discussion of this topic is beyond the scope of this chapter, but the reader is directed to the excellent reviews by Thornber[1] and Lipinski[2] where numerous examples of successful isosteric and bioisosteric replacements are listed.

3 CONFORMATIONAL RESTRICTION

In contrast to bioisosterism, which is intended to retain biological activity by replacement of either binding or non-binding functionalities, conformational restriction retains all the key binding functionalities intact, but seeks to fix their relative positions in the 'active' conformation.

There are many examples of highly conformationally restrained natural products which have been used as medicaments. Two such examples are morphine, which contains the key side chain binding functionalities of enkephalin, and the penicillins, which mimic the acyl-D-Ala-D-Ala of the bacterial cell wall peptidoglycan. Indeed one of the earlier approaches used in medicinal chemistry was to take highly conformationally restrained polycyclic natural products, and by simplification identify novel systems which retained many of the properties of the complex natural product, but were synthetically more amenable. The benzomorphan and piperidine analgesics are such examples derived from morphine.

However, many leads that are identified are small, flexible molecules or peptides which exist in many conformations. In these instances, conformational restriction can be a very powerful tool for lead optimisation to achieve the ultimate objective of identifying a potential drug. Conformational restriction can be achieved in a number of ways; by simple introduction of a methyl group which sterically restricts free bond rotation, by use of intramolecular hydrogen bonds, by introduction of unsaturation which fixes the relative positions of the terminal and geminal substituents due to the non-rotatability of a double bond, or by cyclisation, which fixes the relative position of the substituents either exocyclic or